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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,528	10/13/2000	David M. Stern	0575/62096/JPW/JML	8939

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John P. white
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,528	STERN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 8-23-04 has been entered. Claims 3, 11, 13 and 14 have been amended. Claims 3-5 and 11-14 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 3-5 and 11-14 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat with murine soluble RAGE (sRAGE) via intraperitoneal injection, does not reasonably provide enablement for a method for preventing exaggerated restenosis in a diabetic subject by administering to said subject any sRAGE polypeptide other than murine sRAGE in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 5-18-04. Applicant's arguments filed 8-23-04 have been fully considered but they are not persuasive.

Applicants argue that examiner's Official action back in 4-10-02 states that the specification is enabling for preventing exaggerated restenosis in a diabetic subject by administering sRAGE to the subject (e.g. amendment, p. 5-6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-18-04. The statement

in the Official action back in 4-10-02 was the viewpoint back then but the preceding Official action mailed 5-18-04 indicates that the specification fails to provide adequate guidance and evidence for how to prevent exaggerated restenosis in a diabetic subject by administering to said subject any sRAGE derived from various organisms *in vivo*. The specification only discloses reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat with murine sRAGE. The claims encompass using numerous sRAGEs, which have different amino acid sequences, derived from various organisms, such as humans, cows, horses, rats, mice, sheep, other mammals, fishes, insects etc., to prevent exaggerated restenosis in a diabetic subject *in vivo*. No detailed information for the structural feature of sRAGE that contributes to prevent exaggerated restenosis has been provided. Further, the biological function of a polypeptide was unpredictable from mere amino acid sequence at the time of the invention, therefore, it would require one skilled in the art undue experimentation to practice over the full scope of the invention claimed.

3. Claims 3-5 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat with murine soluble RAGE (sRAGE) via intraperitoneal injection, does not reasonably provide enablement for a method for preventing exaggerated restenosis in a diabetic **human** subject by administering to said subject any sRAGE polypeptide in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to a method for preventing exaggerated restenosis in a diabetic subject by administering to said subject, such as a human, a therapeutically effective amount of soluble receptor for advanced glycation endproducts (sRAGE) *in vivo*. Claim 5 specifies the subject has undergone an angioplasty procedure. Claims 11, 12 and 14 specify the administration route of the inhibitor, such as bolus injection, oral administration, i.v., i.p. etc., or via device, such as a stent or an angioplasty balloon. Claim 13 specifies the inhibitor is administered at a rate of about 2 ug/kg/hr to about 100 ug/kg/hr.

The specification discloses reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat having carotid artery balloon injury with soluble RAGE (sRAGE) via intraperitoneal injection.

The claims encompass using numerous sRAGE derived from various organisms, such as humans, cows, horses, rats, mice, sheep, other mammals, fishes, insects etc., to prevent exaggerated restenosis in a diabetic human subject *in vivo*. The specification fails to provide adequate guidance and evidence for how to prevent exaggerated restenosis in a diabetic human subject by administering to said subject any sRAGE derived from various organisms *in vivo*.

The claims read on preventing exaggerated restenosis in a diabetic human subject by administering to said subject a therapeutically effective amount of sRAGE. The biological environments in different organisms differ from each other physically and physiologically. Even if the sRAGE can function to prevent exaggerated restenosis in animal model, the data from animal model can not be extrapolated into success in preventing exaggerated restenosis in human.

The prior art teaches that successful application of restenosis treatments in small animal models is not predictive of success in other animals, particularly in humans. Muller et al., 1992 (J. Amer. Coll. Cardiol. 19(2):418-432) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies (e.g. abstract). Muller further teaches that the amount of elastin in the media of coronary arteries of larger animals, such as dogs, pigs and baboons, are very similar to that of the human coronary artery but greater than that in small species, such as rodents and fowls, and thickness of the arterial intima varies among species (e.g. p. 420, left column). "Rat arteries differ morphologically from human arteries in that they have no vasa vasorum, have a very much thinner subintimal layer and have a relatively small elastin content in the media (e.g. p. 421, left column, lines 4-7).

Reilly et al., 1993 (Drug Dev. Res. 29(2): 137-147) teach that the angioplasty procedure performed in the rat model used in the instant invention differs from the procedure applied in humans. Reilly teaches that in humans, angioplasty is performed on preexisting atherosclerotic plaques in the coronary artery, whereas it is performed on normal carotid arteries, with lower

shear forces and exposure times, in the rat model (e.g. p. 144, left column). "Thus, important mechanistic features of restenosis may differ between rats and humans" (e.g. p. 144, right column, lines 2-4). Furthermore, Reilly reports that results from a published clinical trial, MERCATOR, raises the possibility that the rat model is not predicative of human restenosis. Cilazapril, an ACE inhibitor, can inhibit neointimal thickening in the rat model but has no effect on restenosis in humans (e.g. p. 144, right column, second paragraph).

Lafont et al (Card. Res. 39(1): 50-59, 7/1998) substantiate the teachings of Reilly, and expand on the reasons that rat restenosis model is deficient. Lafont reiterates that the rat model uses a normal, not a diseased artery, and does not reflect human angioplasty because it utilizes a type of balloon which stretches the artery in a different way than an angioplasty balloon. Lafont also teaches that the resulting lesion is histologically unlike human atherosclerosis because it lacks calcification and calcium deposits, and because it occurs in an otherwise normal artery (page 52, left column, lines 3-12). In conclusion, Lafont indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." (e.g. page 54, right column, lines 3-11).

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use a sRAGE derived from various organisms to prevent exaggerated restenosis in a human. Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working

examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER